Asymmetric Ring-Closing Metathesis: Kinetic Resolution Catalyzed by a Chiral Molybdenum Alkylidene Complex

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Ring-closing metathesis (RCM) catalyzed by transition metal alkylidenes has become a powerful strategy for organic synthesis.[1] Despite significant recent developments in this field, there are very few reports concerning the asymmetric variants of this reaction.[2] Alkylidene complexes of the group VI metals are well-defined catalysts employed in olefin metathesis reactions.[3] We have recently developed a new chelating chiral diol ligand (1*S*,2*S*)- and (1*R*,2*R*)-2′, 2′, 2″, 2″-tetrakis(trifluoromethyl)-1,2-bis(2′-hydroxyethyl)cyclopentane (TBEC-H_2, **1**) and its derived chiral molybdenum alkylidene complex (*R*,*R*)-Mo(CHCMe$_2$Ph)(NAr)(TBEC) (**2**, Ar = 2,6-*i*-Pr$_2$C$_6$H$_3$), in which one face of the Mo−C double bond is blocked by the ligand substituents (Figure 1).[4] Employing **2** as a catalyst, we have observed the first example of the asymmetric RCM.

To explore the possibility of asymmetric induction by **2**, we selected kinetic resolution in RCM. As shown in Scheme 1, RCM consists of two steps. We presumed the second step (ring-closing step) to be suitable for asymmetric induction, as this step involves diastereomeric cyclic transition states that would likely be of different energy.[5] Thus, if k_2(a) and k_2(b) are sufficiently different and slower than k_1 and k_{-1}, kinetic resolution could be observed.

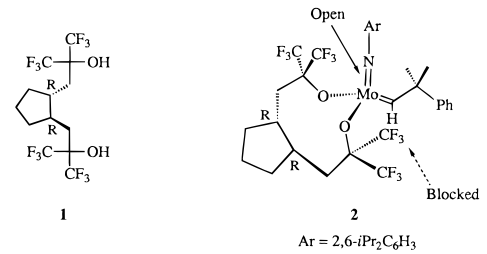
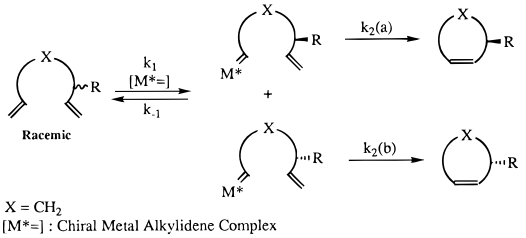


Figure 1. (*R*,*R*)-TBEC-H2 (**1**) and (*R*,*R*)-MoTBEC (**2**).

Scheme 1



For the substrates, we chose dienes that contain a trisubstituted olefin moiety to slow the cyclization step as well as to control the site of first metathesis.[6] Results are summarized in Table 1.

At 25 °C, racemic (6*E*)-5-acetoxy-6-methyl-1,6-octadiene (**3a**) was cyclized rapidly by addition of 2.0 mol % **2** (entry 1). The reaction was quenched after 20 min, at which time 90% of **3a** was consumed. The unreacted **3a** (10%) was recovered, and enantiomeric excess (ee) was determined to be 84%.[7] The configuration was determined to be S.[8] The coordinating solvent THF slowed the reaction, but the efficiency of the kinetic resolution was not improved (entry 2). The progress of the reaction can be followed by lowering the reaction temperature (entries 3−6). From these results, the ratio k_2(fast)/k_2(slow) was calculated to be 2.02.[11] Changing the protecting group to a non-coordinating triethylsilyl group resulted in acceleration of the reaction.[12] The kinetic resolution of **3b** could be carried out at −20 °C, but efficiency and configuration remained constant (entry 7). We also examined the effect of location of the chiral center. By changing the position of the triethylsiloxy group from 5- to 3-, the reaction rate decreased significantly and ee decreased slightly (entry 8).[13,14]

Our working models for five-membered ring formation are shown in Figure 2.[15] For these cases, the (*S*)-isomer has steric

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(2) Applications of chiral metathesis catalysts are found only in the stereoregulation of ring-opening metathesis polymerization: (a) McConville, D. H.; Wolf, J. R.; Schrock, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 4413−4414. (b) O'Dell, R.; McConville, D. H.; Hofmeister, G. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 3414−3423. (c) Heppert, J. A.; Dietz, S. D.; Eilerts, N. W.; Henning, R. W.; Morton, M. D.; Takusagawa, F. *Organometallics* **1993**, *12*, 2565−2572.

(3) Molybdenum: (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886. (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899−6907. (c) Bazan, G. C.; Schrock, R. R.; Cho, H.-N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495−4502. (d) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287−2289. (e) Schrock, R. R. *Strem Chem.* **1992**, *14*, 1−6. Tungsten: (f) Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423−1435. (g) Schrock, R. R.; DePue, R. T.; Feldman, J.; Yap, K. B.; Yang, D. C.; Davis, W. M.; Park, L.; DiMare, M.; Schofield, M.; Anhaus, J.; Walborsky, E.; Evitt, E.; Kruger, C.; Betz, P. *Organometallics* **1990**, *9*, 2262−2275. (h) Aguero, A.; Kress, J.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1985**, 793−794. (i) Couturier, J.; Paillet, C.; Leconte, M.; Basset, J. M.; Weiss, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 628−631. (j) Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8130−8145. (k) Van der Schaaf, P. A.; Abbenhuis, R. A.; Van der Noort, W. P. A.; De Graaf, R.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; Van Koten, G. *Organometallics* **1994**, *13*, 1433−1444.

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(5) There is the possibility for asymmetric induction in the first metathesis step. However, all the substrate (except **3b**, entry 7) asymmetric centers are located far from the first metathesis site. In the case of **3b**, the steric difference of the triethylsiloxy group and the 3′-methyl-3′-pentenyl group is not considered to be significant.

(6) The first metathesis occurs in the following order: (1) monosubstituted olefin, (2) disubstituted olefin, and (3) trisubstituted olefin; see ref 1f.

(7) **3a** and **4a** could not be separated by column chromatography. After determination of the ratio of **3a** and **4a** by ^{1}H NMR of the reaction mixture, these compounds were hydrolyzed, separated, and converted to the Mosher ester to determine the ee. See supporting information for details.

(8) The absolute configuration of recovered **3a** was determined after derivatization to the Mosher ester and comparison to a sample of known absolute configuration (synthesized by the Sharpless kinetic resolution). See supporting information for details.

(9) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1.

(10) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(11) Balavoine, G.; Moradpour, A.; Kagan, H. B. *J. Am. Chem. Soc.* **1974**, *96*, 5152−5158. See also ref 9.

(12) At 0 °C **3b** cyclized quantatatively in 90 min.

(13) At −20 °C, after 600 min, only 10% of **3c** was consumed.

(14) In the case of (6*E*)-3-acetoxy-6-methyl-1,6-octadiene, the reaction did not proceed due to the intramolecular chelation of the acetate carbonyl to molybdenum. See ref 1b.

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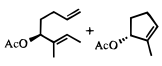
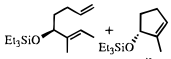
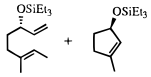
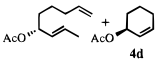
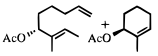
Table 1. (*R,R*)-MoTBEC-Catalyzed Kinetic Resolution in Ring-Closing Metathesis[a,b]

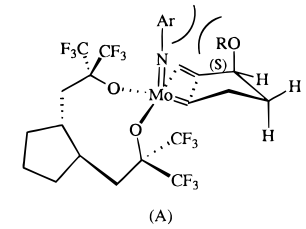
entry	substrate	products	solvent	temp /time(min)	conversion of **3** (%)[c]	unreacted subst. config.[d], e.e.(%)[e]
1	 **3a**	 **4a**	C_6H_6	25°C / 20	90	S, 84
2			THF	25°C / 60	51	S, 36
3			toluene	0°C / 3	21	S, 19
4				0°C / 10	46	S, 29
5				0°C / 90	62	S, 40
6				0°C/ 480	90	S, 78
7	 **3b**	 **4b**	toluene	-20°C / 660	72	S, 48
8	 **3c**	 **4c**	toluene	0°C/ 20	46	S, 22
9[f]	 **3d**	 **4d**	toluene	0°C/ 20	67	R, 22
10[f]	 **3e**	 **4e**	toluene	0°C/ 120	64	R, 26

[a] 2.0 mol % (*R,R*)-MoTBEC was used. [b] Mass balance (yield of cyclic product + recovery of substrate), >90%. [c] Determined by ^{1}H NMR. [d] Determined by synthesis of enantiomerically enriched allyl alcohol by the Sharpless kinetic resolution[9] and derivatization to the Mosher ester.[10] [e] Determined by ^{1}H NMR of Mosher ester derivatized after deprotection. [f] 7.0 mol % (*R,R*)-MoTBEC was used.

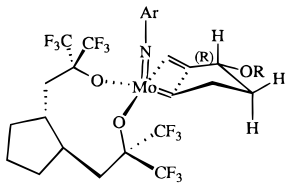
interactions between the pseudo-axial 5-substituent and the bulky imido ligand (A). On the other hand, the (*R*)-isomer does not have such a steric effect (B). Therefore, the (*R*)-isomer is consumed faster than the (*S*)-isomer, resulting in (*S*)-enriched unreacted substrate recovery. In the case of 3-substituted substrates, the (*R*)-isomer has steric interaction between the pseudo-axial 3-substituent and the bulky imido ligand (D), but the (*S*)-isomer has more severe steric repulsion between the pseudo-equatorial 3-substituent and the TBEC ligand (C). Thus, kinetic resolution can be observed due to the faster consumption of the (*R*)-isomer (i.e., recovery of (*S*)-enriched substrate), though ring-closing of 3-substituted substrates is slower in comparison to that of 5-substituted substrates.

Interestingly, kinetic resolution was observed in **3d**, a substrate which possesses a disubstituted olefin instead of a trisubstituted olefin (entry 9).[16] In addition, the enantioselectivity was opposite to that of five-membered ring formation. For six-membered ring formation, the (*R*)-enriched unreacted substrates were recovered (entries 9, 10). Figure 3 shows proposed models for six-membered ring closure. The (*S*)-isomer has its 6-substituent in a pseudoequatorial position in its chairlike transition state (A), whereas the (*R*)-isomer has the substituent in a pseudo-axial position, which causes steric destabilization. Thus, the (*S*)-isomer was consumed faster and the (*R*)-enriched substrate was recovered.

(5-Substituted Substrates)

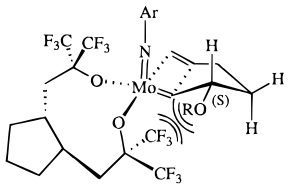


(A)

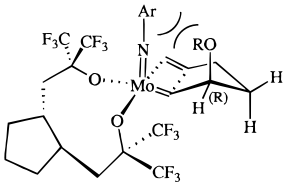


(B)

(3-Substituted Substrates)

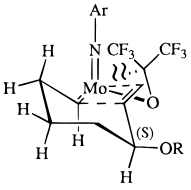


(C)

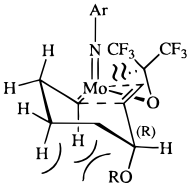


(D)

Figure 2. Proposed models for five-membered ring formation.



(A)



(B)

Figure 3. Partial structures of proposed reaction models for six-membered ring formation.

In summary, we have demonstrated the first asymmetric ring-closing metathesis of dienes by using a newly developed chiral molybdenum alkylidene as catalyst. The improvement of the efficiency of the resolution as well as the scope and limitation of this process are currently under investigation.

Acknowledgment. Support has been provided by Ube Industries, Ltd., Japan (grant to O.F.) and the National Institutes of Health (grant to R.H.G.).

Supporting Information Available: Experimental procedures and full characterization data for reaction products (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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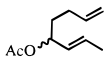
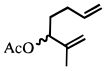
(15) Similar conformatinal models are proposed in intramolecular Ziegler−Natta alkene insertion reactions. See: (a)Young, J. R.; Stille, J. R. *Organometallics* **1990**, *9*, 3022−3025; (b) *J. Am. Chem. Soc.* **1992**, *114*, 4936−4937. (c) Barta, N. S.; Kirk, B. A.; Stille, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 8912−8919.

(16) For five-membered ring formation, no kinetic resolution was observed for **3f**,**g,** which have disubstituted olefin. Reaction conditions: **3f**, 0 °C/20 min, 52% conversion, racemic **3f** was recovered; **3g**, 0 °C/20 min, 54% conversion, racemic **3g** was recovered. This is considered to be due to the faster ring-closing rate compared to those of the substrates containing trisubstituted olefin.



3f



3g